BlueCross BlueShield of Oklahoma

Medical Policies

Medical Policies - Surgery

Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

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Coverage:

CAREFULLY CHECK STATE REGULATIONS AND/OR THE MEMBER CONTRACT

Osteochondral fresh allografting **may be considered medically necessary** for:

- Repair of full-thickness chondral defects of the knee caused by acute or repetitive trauma when other cartilage repair techniques (e.g., microfracture, osteochondral autografting or autologous chondrocyte implantation) would be inadequate due to lesion size, location, or depth.
- Repair of large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) osteochondral lesions of the talus when autografting would be inadequate due to lesion size, depth, or location.
- Revision surgery after failed prior marrow stimulation for large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) osteochondral lesions of the talus when autografting would be inadequate due to lesion size, depth or location.

Osteochondral allografting for all other joints **is considered experimental, investigational and/or unproven**.

Osteochondral autografting, using 1 or more cores of osteochondral tissue, **may be considered medically necessary** for the treatment of**:**

- Symptomatic full-thickness cartilage defects of the knee caused by acute or repetitive trauma in patients who have had an inadequate response to a prior surgical procedure, when ALL of the following criteria have been met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., ≥15 years). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty (TKA) or other reconstructive knee surgery (e.g., ≤55 years); and
  - Focal, full-thickness (grade III or IV) unipolar lesions the weight-bearing surface of the femoral condyles, trochlea or patella that are between 1 cm^2 and 2.5 cm^2 in size; and
  - Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect; and
  - Normal knee biomechanics, or alignment and stability achieved concurrently with osteochondral grafting; and
  - Body mass index (BMI) is ≤ 35 kg/m^2.
- Large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) osteochondral lesions of the talus.
- Revision surgery after failed marrow stimulation for osteochondral lesion of the talus.

Outerbridge Grading	
Grade 0	Normal appearing cartilage
Grade I	Swelling and Softening or Articular Cartilage
Grade II	Fissuring within softened areas
Grade III	Fibrillation
Grade IV	Destruction of articular cartilage and exposed bone

DOCUMENTATION Required for Review of Injury and Prior Treatment/Therapies:

• Progress report, history, and/or operative notes confirming injury and prior treatments/therapies; AND

• Report(s) of standing x-rays documenting normal alignment and stability of the knee and the absence of inflammatory arthritis (e.g., rheumatoid arthritis); AND

• Report(s) from knee arthroscopy showing the presence of the cartilage defect and normal cartilage surrounding the defect.

NOTE 1: Osteochondral autografts or allografts may be performed for treatment of focal articular cartilage lesions in combination (either concurrently or sequentially) with meniscal allografts. For criteria to determine medical necessity of other concurrent or sequential procedures, please refer to the following medical policy, SUR705.034, Meniscal Allografts and Other Meniscal Implants.

NOTE 2: Additional procedures, such as repair of ligaments or tendons of an osteotomy for realignment (includes misalignment and instability) may be performed at the same time of the osteochondral autografting or allografting procedure.

Osteochondral autografting for all other joints and any indications other than those listed above **is considered experimental, investigational and/or unproven**.

Treatment of focal articular cartilage lesions with autologous minced/particulated cartilage **is considered experimental, investigational and/or unproven**.

Treatment of focal articular cartilage lesions with allogeneic minced cartilage **is considered experimental, investigational and/or unproven**.

Treatment of focal articular cartilage lesions with decellularized osteochondral allograft plugs (e.g., Chondrofix) **is considered experimental, investigational and/or unproven**.

Treatment of focal articular cartilage lesions with reduced osteochondral allograft discs (e.g., ProChondrix, Cartiform) **is considered experimental, investigational and/or unproven**.

Description:

Osteochondral grafts are used in repair of full-thickness chondral defects involving a joint. In the case of osteochondral autografts, one or more small osteochondral plugs are harvested from non-weight-bearing sites, usually from the knee, and press fit into a prepared site in the lesion. Osteochondral allografts are typically used for larger lesions. Autologous or allogeneic minced cartilage, decellularized osteochondral allograft plugs, and reduced osteochondral allograft discs are also being evaluated as a treatment of articular cartilage lesions.

Articular Cartilage Lesions

Damaged articular cartilage can be associated with pain, loss of function, and disability, and can lead to debilitating osteoarthrosis over time. These manifestations can severely impair an individual's activities of daily living and quality of life. The vast majority of osteochondral lesions occur in the knee with the talar dome and capitulum being the next most frequent sites. The most common locations of lesions are the medial femoral condyle (69%), followed by the weight-bearing portion of the lateral femoral condyle (15%), the patella (5%), and trochlear fossa. (1) Talar lesions are reported to be about 4% of osteochondral lesions. (2) Autologous or allogeneic grafts of osteochondral or chondral tissue have been proposed as treatment alternatives for patients who have clinically significant, symptomatic, focal defects of the articular cartilage. It is hypothesized that the implanted graft's chondrocytes retain features of hyaline cartilage that is similar in composition and property to the original articulating surface of the joint. If true, the restoration of a hyaline cartilage surface might restore the integrity of the joint surface and promote long-term tissue repair, thereby improving function and delaying or preventing further deterioration.

<u>Treatment</u>

There are 2 main goals of conventional therapy for patients who have significant focal defects of the articular cartilage: symptom relief and articular surface restoration.

First, there are procedures intended primarily to achieve symptomatic relief: débridement (removal of debris and diseased cartilage), and rehabilitation. Second, there are procedures intended to restore the articular surface. Treatments may be targeted to the focal cartilage lesion and most such treatments induce local bleeding, fibrin clot formation, and resultant fibrocartilage growth. These marrow stimulation procedures include: abrasion arthroplasty, microfracture, and drilling, all of which are considered standard therapies.

Microfracture

Efficacy of the microfracture technique for articular cartilage lesions of the knee was examined in a 2009 systematic review. (3) Twenty-eight studies (total N=3122 patients) were selected; 6 studies were randomized controlled trials (RCTs). Microfracture was found to improve knee function in all studies during the first 24 months after the procedure, but the reports on durability were conflicting. A prospective longitudinal study of 110 patients by Solheim et al. (2016) found that, at a mean of 12 years (range, 10-14 years) after microfracture, 45.5% of patients had poor outcomes, including 43 patients who required additional surgery. (4) The size of the lesion has also been shown to have an effect on outcomes following marrow stimulation procedures.

Abrasion

Fibrocartilage is generally considered to be less durable and mechanically inferior to the original articular cartilage. Thus various strategies for chondral resurfacing with hyaline cartilage have been investigated. Alternatively, treatments of very extensive and severe cartilage defects may resort to complete replacement of the articular surface either by osteochondral allotransplant or artificial knee replacement.

Osteochondral Grafting

Both fresh and cryopreserved allogeneic osteochondral grafts have been used with some success, although cryopreservation decreases the viability of cartilage cells, and fresh allografts may be difficult to obtain and create concerns regarding infectious diseases. As a result, autologous osteochondral grafts have been investigated as an option to increase the survival rate of the grafted cartilage and to eliminate the risk of disease transmission. Autologous grafts are limited by the small number of donor sites; thus allografts are typically used for larger lesions. In an effort to extend the amount of the available donor tissue, investigators have used multiple, small osteochondral cores harvested from non-weight-bearing sites in the knee for treatment of full-thickness chondral defects. Several systems are available for performing this procedure: the Mosaicplasty System (Smith and Nephew), the OATS (Osteochondral Autograft Transfer System; Arthrex), and the COR and COR2 systems (DePuy Mitek).

Although mosaicplasty and autologous osteochondral transplantation (AOT) may use different instrumentation, the underlying mode of repair is similar (i.e., use of multiple osteochondral cores harvested from a non-weight- bearing region of the femoral condyle and autografted into the chondral defect). These terms have been used interchangeably to describe the procedure.

Preparation of the chondral lesion involves débridement and preparation of recipient tunnels. Multiple individual osteochondral cores are harvested from the donor site, typically from a peripheral non-weight- bearing area of the femoral condyle. Donor plugs range from 6 to 10 mm in diameter. The grafts are press fit into the lesion in a mosaic-like fashion into the same-sized tunnels. The resultant surface consists of transplanted hyaline articular cartilage and fibrocartilage, which is thought to provide "grouting" between the individual autografts. Mosaicplasty or AOT may be performed with either an open approach or arthroscopically. Osteochondral autografting has also been investigated as a treatment of unstable osteochondritis dissecans lesions using multiple dowel grafts to secure the fragment. While osteochondral autografting is primarily performed on the femoral condyles of the knee, osteochondral grafts have been used to repair chondral defects of the patella, tibia, and ankle. With osteochondral autografting, the harvesting and transplantation can be performed during the same surgical procedure. Technical limitations of osteochondral autografting are difficulty in restoring concave or convex articular surfaces, incongruity of articular surfaces that can alter joint contact pressures, short-term fixation strength and load-bearing capacity, donor-site morbidity, and lack of peripheral integration with peripheral chondrocyte death.

Reddy et al. (2007) evaluated donor-site morbidity in 11 of 15 patients who had undergone graft harvest from the knee (mean, 2.9 plugs) for treatment of osteochondral lesions of the talus. (5) At an average 47-month follow-up (range, 7-77 months), 5 patients were rated as having an excellent Lysholm Knee Scale score (95-100 points), 2 as good (84-94 points), and 4 as poor (≤64 points). Reported knee problems were instability in daily activities, pain after walking 1 mile or more, slight limp, and difficulty squatting. Hangody et al. (2001) reported that some patients had slight or moderate complaints with physical activity during the first postoperative year, but there was no long-term donor-site pain in a series of 36 patients evaluated 2 to 7 years after AOT. (6)

Filling defects with minced articular cartilage (autologous or allogeneic) is another single-stage procedure being investigated for cartilage repair. The Cartilage Autograft Implantation System (CAIS; Johnson and Johnson) harvests cartilage and disperses chondrocytes on a scaffold in a single-stage treatment. BioCartilage (Arthrex) consists of a micronized allogeneic cartilage matrix that is intended to provide a scaffold for microfracture. DeNovo NT Graft (Natural Tissue Graft) is produced by ISTO Technologies and distributed by Zimmer. DeNovo NT consists of manually minced cartilage tissue pieces obtained from juvenile allograft donor joints. The tissue fragments are mixed intraoperatively with fibrin glue before implantation in the prepared lesion. It is thought that mincing the tissue helps both with cell migration from the extracellular matrix and with fixation.

A minimally processed osteochondral allograft (Chondrofix; Zimmer) is now available. Chondrofix is composed of decellularized hyaline cartilage and cancellous bone; it can be used "off the shelf" with precut cylinders (7-15 mm). Multiple cylinders may be used to fill a larger defect in a manner similar to AOT or mosaicplasty.

ProChondrix (AlloSource) and Cartiform (Arthrex) are wafer-thin allografts where the bony portion of the allograft is reduced. The discs are laser etched or porated and contain hyaline cartilage with chondrocytes, growth factors, and extracellular matrix proteins. ProChondrix is available in dimensions from 7 to 20 mm and is stored fresh for a maximum of 28 days. Cartiform is cut to the desired size and shape and is stored frozen for a maximum of 2 years. The osteochondral discs are typically inserted after microfracture and secured in place with fibrin glue and/or sutures.

Autologous chondrocyte implantation is another method of cartilage repair involving the harvesting of normal chondrocytes from normal non-weight-bearing articular surfaces, which are then cultured and expanded in vitro and implanted back into the chondral defect. Autologous chondrocyte implantation techniques are discussed in medical policy SUR705.035.

Regulatory Status

According to the manufacturer, the device is considered a class I device by the U.S. Food and Drug Administration (FDA) and is exempt from 510(k) requirements. This classification does not require submission of clinical data regarding efficacy but only notification to the FDA prior to marketing.

FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Osteochondral grafts are included in these regulations.

DeNovo® ET Live Chondral Engineered Tissue Graft (Neocartilage) is marketed by ISTO Technologies outside of the United States. The FDA approved ISTO's investigational new drug application for Neocartilage in 2006, which allowed ISTO to pursue phase 3 clinical trials of the product in human subjects.

Rationale:

This medical policy was originally created in 2001 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 5, 2017.

Assessment of the efficacy for a therapeutic intervention involves a determination whether an intervention improves health outcomes compared to available alternatives. The optimal study design for this purpose is a randomized controlled trial (RCT) that compares the therapeutic intervention with existing alternative treatments and includes clinically relevant measures of health outcomes. It is recognized that RCTs are extremely important to assess treatments of cartilage repair procedures, due to the expected placebo effect and the subjective nature of pain. The present review focuses on

cartilage repair procedures of the knee, ankle, elbow, and shoulder using allografts and autografts compared to débridement, marrow- stimulating procedures, and autologous chondrocyte implantation (ACI). The following is a summary of key references to date.

Osteochondral Autograft for Articular Cartilage Lesions of the Knee

The evidence on osteochondral autograft transplantation (AOT) for articular cartilage lesions of the knee includes systematic reviews and a number of RCTs that have compared outcomes from AOT with marrow stimulation or ACI.

Systematic Reviews

A 2016 Cochrane review by Gracitelli et al. evaluated surgical interventions (microfracture, drilling, AOT, allograft transplantation) for the treatment of isolated cartilage defects of the knee in adults. (7) Three RCTs selected compared AOT to microfracture for isolated cartilage defects. The evidence was considered of very low quality with high or unclear risk of bias.

In a 2008 systematic review, at short-term follow-up, neither of the "advanced" cartilage repair techniques (osteochondral transplantation or autologous chondrocyte transplantation) showed superior outcomes compared with traditional abrasive techniques. (8) Based on evidence from 5 RCTs and 1 prospective comparative trial, Magnussen et al. concluded that no single technique produced superior clinical results for treatment of articular cartilage defects, however, "any differences in outcome based on the formation of articular rather than fibrocartilage in the defect may be quite subtle and only reveal themselves after many years of follow-up. Similarly, complications such as donor-site morbidity in AOT may be late in their presentation and thus not be detected at short follow-up." However, in a mid-term meta-analysis that included 5 RCTs (described below), Pareek et al. (2016) found that Tegner Activity Scale (TAS) scores were higher and failure rates lower with AOT than with to microfracture. (9) In subgroup analysis, activity scores were higher in the subset of patients treated with AOT who had lesions greater than 3 cm^2 at mid-term follow-up.

In a 2011 systematic review, Harris et al. evaluated whether outcomes from cartilage repair or restoration techniques remained successful if combined with meniscal allograft. (10) Six level IV studies (case series) with 110 patients were included in the review. Patients underwent meniscal allograft transplantation with ACI (n=73), osteochondral allograft (n=20), AOT (n=17), or microfracture (n=3). All studies showed improved clinical outcomes at final follow-up compared with the preoperative condition. Outcomes were also compared with historical outcomes of each procedure performed in isolation. Four of the 6 studies found outcomes equivalent to procedures performed in isolation, suggesting that the combined procedures did not result in poorer outcomes.

Subsection Summary: Systematic Reviews

Several systematic reviews have evaluated osteochondral autografting for cartilage repair. Evidence is of low quality, and not all reviews found a benefit compared to abrasion techniques. However, there is evidence that, in patients with larger lesions and longer follow-up, treatment with osteochondral autografts decreases failure rates compared with abrasion techniques (e.g., microfracture, drilling).

<u>Randomized Controlled Trials</u>

Osteochondral Autografts vs Marrow Stimulation

Studies included in the systematic reviews described above included 3 RCTs from the same group of investigators, 1 RCT with mid-term follow-up, and 1 RCT with long-term follow-up; they compared AOT to microfracture. These RCTs are detailed below.

Gudas et al. (2005) reported on a blinded comparison of arthroscopic AOT with microfracture for lesions of the femoral condyle (1-4 cm^2) in 60 athletes between 15 and 40 years of age (mean, 24.3 years). (11) Follow-up with 95% of the athletes for up to 3 years after surgery showed that more athletes returned to sports activities (mean, 6.5 months) following AOT (93% vs 52%) and fewer required revision (1 of 28 vs 9 of 29), both respectively. Overall, 96% of patients treated by AOT had an excellent or good result compared with 52% treated by microfracture. At 1-year follow-up, scores on the International Cartilage Repair Society (ICRS) cartilage grading system were higher in the AOT group and, at 3-year follow-up, results from the Harris Hip Score (HSS) improved more in the AOT group. Blinded arthroscopic and histologic assessment in a subset of patients showed hyaline cartilage of normal appearance following transplantation, whereas microfracture frequently resulted in surface fibrillation and soft fibroelastic tissue. At 10-year follow-up, there were 4 (14%) failures in the AOT group and 11 (38%) failures in the microfracture group. (12) TAS scores decreased in both groups over time, but remained significantly better following AOT than microfracture. In the subgroup of patients younger than 25 years of age at the time of surgery, 15 (75%) of 20 in the AOT group and 8 (37%) of 22 in the microfracture group maintained the same level of activity (competitive athletes or frequently sporting) as before the injury. The level of sporting activity was reported to decrease in older patients because of age or reasons unrelated to their knee injuries.

Another report by Gudas et al. (2013) compared mosaicplasty to microfracture or débridement. One hundred two patients with lesions associated with anterior cruciate ligament (ACL) injury were randomized to 1 of the 3 procedures to repair their ACLs. (13) A matched control group of 34 patients with ACL injury but no articular cartilage lesion was included as a comparator. The postoperative rehabilitation protocol was the same for the 3 treatment groups. At a mean 36.1-month follow-up, patients were evaluated with the International Knee Documentation Committee (IKDC) score, TAS score, and clinical assessment. All groups showed a significant improvement in the IKDC score compared with before surgery. Patients without cartilage lesions had significantly better IKDC subjective scores than patients with cartilage lesions. For the 3 groups with cartilage lesions, the mosaicplasty group's IKDC subjective knee evaluation was significantly better than those for the

microfracture or débridement groups, although the differences between the groups were modest. TAS scores were similar for the mosaicplasty (7.1) and microfracture (6.9) groups, and slightly lower for the débridement group (6.2).

Gudas et al. (2009) also published a randomized trial of AOT (n=25) versus microfracture (n=25) in children 12 to 18 years of age (mean, 14.3 years). (14) Only children with grade 3 or 4 osteochondritis dissecans (OCD) defects of the femoral condyles were selected. The OCD defects were between 2 and 4 cm^2 in area, and the mean duration of symptoms was 24 months. Follow-up was obtained in 94% of patients. After 1 year, the proportion of excellent-to-good outcomes was similar for the 2 groups (92% for AOT vs 86% for microfracture). However, after a mean 4.2 years of follow-up (range, 3-6 years), the microfracture group showed 9 (41%) of 22 failures. By comparison, there were no failures in the AOT group, and good-to-excellent outcomes were obtained in 83% of the children. Magnetic resonance imaging (MRI) at a mean of 18 months after surgery showed no evidence of graft loosening or migration, with excellent or good repair in 19 (91%) of 21 children. By comparison, blinded evaluation showed excellent or good repair in 10 (56%) of 18 children after microfracture.

In 2012, Lim et al. reported on an RCT comparing AOT (n=22), ACI (n=18), and microfracture (n=30). (15) Outcomes were measured using the Lysholm Knee Scale (LKS), TAS, and HSS. All 3 procedures showed improvement in functional scores, with no significant differences between the groups. Arthroscopy at 1 year showed excellent or good results in about 80% of patients.

In 2014, Ulstein et al. reported on a long-term randomized trial (median, 9.8 years; range, 4.9-11.4 years) comparing AOT to microfracture. (16) This smaller study enrolled 25 patients with a lesion of the femoral condyle or trochlea, with an area between 2 and 6 cm^2. There were no significant differences between the AOT and microfracture groups in patient-reported outcomes (LKS, Knee Injury and Osteoarthritis Outcome Score [KOOS]), muscle strength, or radiologic outcome). However, 4 of 11 patients in the microfracture group underwent a second cartilage procedure compared with none in the AOT group.

Subsection Summary: Osteochondral Autografts vs Microfracture

We identified 5 RCTs that compared osteochondral autografting with microfracture. They are summarized in the systematic reviews. Although the quality of the studies is not high, there is evidence of lower rates of reoperation and higher activity levels, particularly in patients with larger lesions and at longer follow-up, when treated with osteochondral autografting. A limitation of this body of evidence is that most data came from a single research group.

Osteochondral Autografts vs ACI

Several RCTs have compared AOT to ACI for the treatment of articular cartilage lesions. Bentley et al. (2003) randomized 100 consecutive patients with larger symptomatic lesions of the knee (average, 4.7 cm^2; range, 1-12 cm^2) to ACI or mosaicplasty. (17) Seventy-four percent of lesions were on the

femoral condyle and 25% were on the patella. Ninety-four patients had had previous surgical interventions, and the average duration of symptoms before surgery was 7 years. Clinical assessment at 1 year showed excellent or good results in 98% of the ACI patients and 69% of the mosaicplasty patients. The mosaicplasty plugs showed incomplete healing of the spaces between the grafts, fibrillation of the repair tissue, and disintegration of the grafts in some patients. The lack of healing might have been related to both the relatively large lesion size and the unusual prominent placement of the plugs in this study, which was intended to allow contact with the opposite articular surface. With 6 patients lost to follow-up at a minimum 10 years after the index surgery, repair was found to have failed in 17% of patients treated with ACI and 55% of patients treated with mosaicplasty. (18)

Dozin et al. (2005) reported results from a multicenter RCT that compared ACI with AOT. (19) Forty-four subjects, who had a focal, symptomatic chondral injury of Outerbridge grade III or IV with no previous surgical treatment, were randomized to ACI or to AOT 6 months after undergoing arthroscopic débridement. Average lesion size was 1.9 cm. There was a high dropout rate, with only about 50% of patients undergoing the procedure; 10 patients were cured by débridement. With intention-to-treat analysis, the percentages of patients who achieved complete success were 88% (16/18 evaluable cases) in the AOT arm versus 68% (13/19 evaluable cases) in the ACI arm (p=0.093). The high rate of spontaneous improvement after simple débridement raises questions about the appropriateness of additional surgical intervention in patients with small lesions similar to those included in this trial.

Horas et al. (2003) reported 2-year follow-up in a study of 40 patients (age range, 18-42 years) with an articular lesion of the femoral condyle (size range, 3.2-5.6 cm^2) who were randomized to ACI or AOT. (20) Eleven (28%) had had prior surgical treatment. Authors reported that both treatments improved symptoms (85% of each group), although those in the AOT group responded more quickly. Histomorphologic evaluation of 5 biopsy specimens at 2 years or less after transplantation indicated that the osteochondral cylinders had retained their hyaline character, although investigators noted a persistent interface between the transplant and the surrounding original cartilage.

Subsection Summary: Osteochondral Autografts vs ACI

Of 3 RCTs identified that compared AOT with ACI, interpretation of 2 is limited. The study by Bentley et al. might have been affected by the use of prominent plugs, while the study by Dozin et al. included patients with smaller lesions, many of whom did not proceed to surgery. The third RCT included 40 patients with larger lesions (3.2-5.6 cm^2) and reported similar improvements in symptoms for the 2 treatments.

Observational Studies

While observational studies do not provide evidence of efficacy or comparative efficacy, they may provide information about the durability of any observed improvements and potential impacts of patient selection factors. Observational studies have reported longer term outcomes and an impact of

sex, age, and size and location of the lesion.

Hangody, who first reported use of the mosaicplasty technique in humans in 1992, has coauthored a number of summaries and case series. (21-23) A 2008 summary paper included descriptions of a prospective multicenter comparison of 413 resurfacing procedures and follow-up from 1097 mosaicplasties at the authors' institution. (23) Although authors reported that the comparative study found hyaline-like resurfacing to result in a better clinical outcome than other techniques, the cited study is not publicly available in a peer-reviewed publication. For the retrospective analysis, Hangody et al. reported 789 implantations on the femoral condyles, 147 in the patellofemoral joint, 31 on the tibia condyles, 98 on talar domes, 8 on the capitulum humeric, 3 on humeral heads, and 11 on femoral heads. Clinical scores at long-term follow-up suggested good-to-excellent results in 92% of patients with femoral condylar implantations, 87% of tibial resurfacings, and 74% of patellar and/or trochlear mosaicplasty. (AOT for talar procedures is described in a separate section below.) Based on their experience with this procedure, Hangody et al. considered the optimal indications to be lesions 1 to 4 cm^2 in diameter, patients 50 years of age or younger (due to decreased repair capacity with aging), and correction of instability, malalignment, and meniscal or ligamental tears. (23)

Ollat et al. (2011) reported on a retrospective multicenter study from the French Society of Arthroscopy that included 142 patients at a mean follow-up of 8 years. (24) (This technique has been used extensively in France due to restrictive legislation on restoration techniques, including chondrocyte transfer.) Mean lesion size was 2.29 cm^2, and mean number of plugs was 4 (range, 1-14 plugs). Most patients (81.8%) were satisfied or very satisfied with their functional outcomes and there was significant improvement in the ICRS, IKDC function, and Hughston scores at follow-up. Factors for a good prognosis were: male sex, location of the defect in the medial femoral condyle, OCD, deep, small defects, and a short interval before surgery.

Solheim et al. (2010, 2013) reported 5- to 9-year (N=69) and 10- to 14-year (N=73) follow-up from patients treated for articular cartilage defects 1 to 5 cm^2 in area. (25, 26) The Lysholm Knee Scale (LKS) score improved from 49 at baseline to 72 at mid-term and long-term follow-up. Visual analog scale (VAS) scores for pain improved from 58 at baseline to 27 at mid-term follow-up and 33 at long-term follow-up. However, a poor outcome, defined as a LKS score of 64 or less or subsequent knee replacement, was observed in 40% of the patients by 10 to 14 years. Factors associated with a poor outcome were patient age (≥40 years at the time of surgery), female sex, and articular cartilage defects of 3 cm^2 or more. The failure rate was 83% for females 40 years or older with a defect area of 3 cm^2 or more compared to 12.5% for males younger than 40 years old with an articular cartilage defect less than 3 cm^2.

Other reports have focused on AOT for treating patellar lesions. In 2014, Astur et al. prospectively analyzed 33 patients with symptomatic patellar lesions (diameter, 1-2.5 cm) treated with AOT. (27) At a minimum 2-year follow-up (range, 24-54 months), all patients were reported to have significant improvement in functional scores, as measured by the LKS, Kujala, and Fulkerson scores and the 36-

Item Short-Form Health Survey quality of life score. Nho et al. (2008) reported average 29-month follow-up following patellar resurfacing with osteochondral autografts in 22 patients. (28) Mean lesion size was 1.6 cm^2, filled with an average of 1.8 plugs per defect. The IKDC score improved from 47 preoperatively to 74 at follow-up. The activity of daily living score increased from 60 preoperatively to 85 at follow-up.

The importance of concomitant realignment procedures is addressed by other studies. Laprell and Petersen (2001) reported 6- to 12-year follow-up for 29 (83%) of 35 patients with severe osteochondral defects (77% with OCD) who were treated by AOT. (29) Average age of the patients at the time of surgery was 26 years. Clinical evaluation at an average of 8 years after the procedure found 12 (41%) patients to be normal, 14 (48%) as nearly normal, and 3 (10%, all of whom refused correction of malalignment) as abnormal. Another report (2007) described 7-year follow-up for 30 patients treated with AOT for symptomatic grade III to IV chondral lesions (average, 1.9 cm; range, 1.0-2.5 cm). (30) Nineteen patients received other procedures (ACL reconstruction, meniscectomy, medial collateral ligament repair) at the same time. MRI at 7 years showed complete bone integration in 96% of patients, complete integration of the grafted cartilage in 75% of cases, complete filling of the cartilage defect in 63%, and congruency of the articular surface in "some" patients.

Subsection Summary: Observational Studies

A number of observational studies have provided additional information with longer follow-up and factors (i.e., patient age at the time of surgery, lesion size, location of lesion) associated with outcomes after treatment with osteochondral autografts. Overall, these studies have indicated that outcomes of osteochondral autografting are superior in younger male patients who have lesions smaller than 3 cm^2. Outcomes are reported to be superior in lesions of the femoral condyles, although treatment of patellar lesions has also been reported to improve pain and function.

Section Summary: Osteochondral Autograft for Articular Cartilage Lesions of the Knee

Several systematic reviews of RCTs have evaluated AOT for cartilage repair of the knee in the short and mid-term. The RCTs are not high quality, and not all reviews found a benefit compared to abrasion techniques. However, compared to abrasion techniques (e.g., microfracture, drilling), there is evidence that AOT decreases failure rates and improves outcomes in patients with medium size lesions (e.g., 2-6 cm^2) when measured at longer follow-up. This is believed to be due to better durability of the natural hyaline cartilage compared to the fibrocartilage that is obtained with abrasion techniques. The least problematic RCT, which compared AOT to ACI in patients with lesions measuring 3.2 to 5.6 cm^2, found similar improvements in symptoms for both treatments. Factors shown to affect success in observational studies are younger male patients with lesions smaller than 3 cm^2. Thus, there is a relatively narrow range of lesion size for which AOT is most effective. In addition, the best results have been observed with lesions on the femoral condyles, although treatment of trochlea and patella lesions also improves outcomes.

Correction of malalignment is important for success of the procedure.

Fresh Osteochondral Allograft for Articular Cartilage Lesions of the Knee

<u>Systematic Reviews</u>

The 2016 Cochrane review by Gracitelli et al. did not identify any RCTs on fresh allograft transplantation. (7)

A 2015 systematic review by De Caro et al. included 11 articles that had at least 10 patients and were published in the previous 5 years. (31) Articles included a total of 374 knees in 358 patients treated with fresh osteochondral allografting. The size of the lesions ranged from 1 to 27 cm^2. Different outcome measures were used, but overall results showed improvement in objective and subjective clinical scores, a high rate of return to some level of sport or active duty, and graft survival rates of 82% at 10 years and 66% at 20 years. Although bony integration was usually achieved, cartilage integration was limited. In a 2015 review of indications, techniques, and outcomes, Chui et al. stated that fresh osteochondral allografting would be indicated for lesions greater than 2 cm^2 for which other techniques such as microfracture, AOT, and ACI are inadequate due to lesion size, location, or depth. (32) Reviewers also considered fresh osteochondral allografting to be a salvage procedure for previously failed restoration treatments of the knee.

<u>Observational Studies</u>

Long-term outcomes with fresh osteochondral allografting have been reported in other case series. Emmerson et al. (2007) reported mean 7.7-year follow-up (range, 2-22 years) for 66 knees of 64 patients who underwent fresh osteochondral allografting for OCD of the femoral condyle. (33) All patients had undergone previous surgery, with an average of 1.7 prior surgeries per knee. Mean allograft size was 7.5 cm^2. One knee was lost to follow-up. Of the remaining 65 knees, 10 (15%) knees had additional surgery, 47 (72%) were rated good to excellent, and 8 (13%) were rated fair to poor. Kaplan-Meier analysis demonstrated a 91% graft survival rate at 5 years and 76% graft survival rates at 10 and 15 years. The mean D'Aubigne and Postel score improved from 13.0 (fair) preoperatively to 16.4 (good) at the most recent follow-up. Subjective knee function improved from a mean of 3.4 to 8.4 on a 10-point scale.

Gross et al. (2005) reported on a minimum 5-year follow-up in a series of 60 patients who received femoral condylar grafts and 65 patients who received tibial plateau grafts for knee defects. (34) Eligible allograft recipients were younger than 60 years and had traumatic unipolar osteochondral defects of at least 3 cm in diameter and 1 cm deep. If the meniscus was also significantly damaged, it was resected and replaced with allograft meniscus. Realignment of the involved leg was also performed to unload the graft. Patients were assessed pre- and postoperatively using the modified HSS. If there were no outcome data in the database within the last 12 months, patients were contacted and a follow-up visit was arranged or a questionnaire administered by telephone. Referring

physicians were also contacted to obtain recent radiographs of the knee. Follow-up was obtained for 86% of patients who received a femoral graft (average, 10 years) and 97% of patients with a tibial graft (average, 11.8 years). For the femoral grafts, 12 failed and required graft removal or conversion to total knee replacement. At the end of the study period, 48 (80%) of the 60 femoral grafts were in situ with an average HSS of 83 out of 100.

Kaplan-Meier analysis showed a 95% graft survival rate at 5 years, 85% at 10 years, and 74% at 15 years. For the tibial grafts, 21 failed at a mean interval of 9.7 years. At the end of the study, 44 (68%) of 65 tibial grafts were in situ and functioning with an HSS greater than 70 points. Survival analysis revealed a 95% graft survival rate at 5 years, 80% at 10 years, and 65% at 15 years.

Fresh osteochondral allografting for patellar cartilage injury was reported by Gracitelli et al. (2015). (35) Of 28 knees (27 patients) that had osteochondral transplantation, 8 (28.6%) were considered failures and 9 (45%) required further surgery. Allograft survival was estimated to be 78.1% at 10 years and 55.8% at 15 years. The mean follow-up duration was 9.7 years (range, 1.8-30.1 years) for the 20 knees (71.4%) with intact grafts.

Section Summary: Fresh Osteochondral Allograft for Articular Cartilage Lesions of the Knee

The evidence on fresh osteochondral allografts for articular cartilage lesions of the knee includes case series and systematic reviews of case series. Due to the lack of alternatives, this fresh allograft procedure may be considered a salvage operation in younger patients for full-thickness chondral defects of the knee caused by acute or repetitive trauma when other cartilage repair techniques (e.g., microfracture, osteochondral autografting, ACI) would be inadequate due to lesion size, location, or depth.

Osteochondral Autograft for Articular Cartilage Lesions of the Ankle

Osteochondral Autograft for Articular Cartilage Lesions of the Ankle Less Than 1.5 cm^2

Osteochondral lesions of the talus are typically associated with ankle sprain or fracture, but comprise a relatively small proportion of lesions (»4%) compared to cartilage lesions of the knee joint. (2) Therefore, RCTs on AOT for talar lesions may be limited. One RCT with 32 patients, case series, and a systematic review of these studies have been identified on AOT for lesions of the talus.

Zengerink et al. published a systematic review on treatment of osteochondral lesions of the talus in 2010. (36) Fifty-one nonrandomized and 1 randomized trial (Gobbi et al., 2006 (37); described below) were included. Studies described a variety of lesion sizes, some cystic, some as primary treatment, and some after a failed arthroscopic procedure, with follow-up of at least 6 months. Success rates averaged 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of ACI and the knee morbidity seen with osteochondral autografting, the

review concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions. However, analysis was not conducted to assess the relation between lesion characteristics and success rates, limiting interpretation of these results.

The following sections review the evidence for lesions that have failed a prior arthroscopic procedure, and for larger lesions, defined as at least 1.5 cm^2 in size. This size threshold is derived from studies that have determined bone marrow stimulation procedures for articular cartilage lesions of the talus that are at least 1.5 cm^2 in area have lower success rates than for those for smaller lesions. (38-40) For lesions less than 1.5 cm^2 in size, multiple studies have shown high success rates with marrow stimulation alone. (41) Because of the increase in morbidity with AOT, marrow stimulation would be the most appropriate treatment for small primary lesions. Of the relatively small number of talar osteochondral lesions, about 20% will be considered too large for marrow stimulation. (38) This series reported by Choi et al. (2009) also estimated that the failure rate following marrow stimulation was 10.5% for lesions less than 1.5 cm^2; whereas 80% of lesions at least 1.5 cm^2 failed after a marrow stimulation procedure.

<u>Subsection Summary: Osteochondral Autograft for Articular Cartilage Lesions of the Ankle Less Than 1.5 cm^2</u>

Multiple studies have reported favorable outcomes with marrow stimulation alone for smaller osteochondral lesions less than1.5 cm^2 in area.

<u>Osteochondral Autograft for the Primary Treatment of Large (>1.5 cm^2) or Cystic Articular (>3.0 cm^3) Cartilage Lesions of the Ankle</u>

Randomized Controlled Trials

The sole RCT identified on AOT for articular cartilage lesions of the talus is by Gobbi et al. (2006). (37) The study included 32 patients with large (mean, ≈4 cm^2; range, 1-8 cm^2) lesions randomized to chondroplasty, microfracture, or AOT. Assessment at 24-month follow-up showed similar improvements (≈40 points) for the 3 treatment groups, as measured by the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score (baseline score, 31-37; an AOFAS score of 90 to100 is considered excellent, 80-89 is good, 70-79 is fair, <70 is poor) and the Subjective Assessment Numeric Evaluation (baseline score, 35-36). Complication rates were also similar. Postoperative pain, measured by numeric pain intensity scores, was greater following AOT (5.25) than after chondroplasty (3.3) or microfracture (3.4). Although authors reported following subjects through a mean of 53 months (range, 24-199 months), durability results after 24 months was not reported. Thus any potential differences between hyaline and fibrocartilage at longer term follow-up cannot be determined from this study.

Observational Studies

In 2014, Haleem et al. reported on a minimum 5-year follow-up for AOT for larger lesions of the talus. (42) Fourteen patients who had a double plug graft for a larger lesion (mean, 208 mm^2; SD=54) were matched by age and sex to a cohort of 28 patients who had a single plug graft for a smaller osteochondral lesion (mean, 74 mm^2; SD=26). Both groups had significant improvements in the Foot and Ankle Outcome Score (FAOS) and 12-Item Short-Form Health Survey scores, with no significant difference between the single-plug and double-plug groups. In the single-plug group, FAOS improved from 51.6 (SD=10.2) at baseline to 87.1 (SD=5.1) at final follow-up, while in the double-plug group the FAOS improved from 49.5 (SD=12.1) to 86.2 (SD=6.5).

In the 2008 report (described above), Hangody et al. reported on a series AOT for knee and ankle and included 98 talar lesions. (23) Good-to-excellent results were reported for 93% of the talar procedures, including durable results over a mean 4.2-year period (range, 2-7 years).The average size of the grafts was 1 cm^2 and an average of 3 osteochondral cores (range, 1-6 cm^2) were used.

Subsection Summary: Osteochondral Autograft for the Primary Treatment of Large (>1.5 cm^2) or Cystic Articular (>3.0 cm^3) Cartilage Lesions of the Ankle

The evidence on AOT for the treatment of large or cystic articular cartilage lesions includes an RCT that found similar efficacy results for AOT, marrow stimulation, and arthroplasty at 2-year follow-up. Longer term results were not reported. For the alternative of marrow stimulation, observational studies have generally reported worse outcomes and high failure rates for large lesions. Thus, there is a rationale for use of osteochondral autograft for larger lesions. This is supported by an observational study that showed good improvement on the FOAS through at least 5-year follow-up using 2 AOT plugs.

Osteochondral Autograft for Treatment of Osteochondral Lesions of the Ankle That Have Failed a Prior Marrow Stimulation Procedure

Nonrandomized Comparative Trials

In 2014, Yoon et al. compared outcomes for 22 patients who underwent AOT to outcomes for 22 patients who underwent repeat arthroscopy with marrow stimulation after failed treatment of osteochondral lesions of the talus. (43) The treatment was selected by the patient after discussion with the surgeon about the risks and benefits of the 2 procedures, including possible nonunion of the osteotomy site, donor-site morbidity, and the recovery period. The study included consecutive patients who met study criteria and had failed primary marrow stimulation. Exclusion criteria were diffuse arthritic changes or diffuse fibrillated articular cartilage or axial malalignment or chronic ankle instability. These 44 patients were among 399 patients who received arthroscopic marrow stimulation during the study period, indicating that, for about 90% of patients, primary marrow stimulation was effective. The 2 groups were comparable at baseline. Independent and blinded evaluation showed an excellent or good outcome on AOFAS scores (≥80) in 19 (86.4%) of patients treated with AOT compared to 12 (54.5%) of patients who received repeat marrow stimulation (p=0.021). All patients

showed initial improvement in the VAS and AOFAS score after 6 months, but, over a mean follow-up of 50 months, only 7 (31.8%) in the repeat marrow stimulation group achieved excellent or good results and 14 (63.6%) of this group underwent further revisions. For patients with large lesions who were treated with repeat microfracture, 100% underwent a subsequent procedure. Conversely, a significantly higher proportion of the group treated with AOT 18 (81.8%) achieved excellent or good results over a mean follow-up of 48 months and none required further revisions.

In 2011, Imhoff et al. retrospectively evaluated 26 AOT procedures (25 patients) of the talus at a mean follow-up of 7 years (range, 53-124 months); 9 of the patients had failed a prior marrow stimulation procedure. (44) Two additional patients had undergone a revision procedure and were not included in the follow-up data. The lesion size was less than 3 cm^2 and an average of 1.5 cylinders was grafted. From baseline to follow-up, AOFAS scores improved from 50 to 78 points (p<0.01), TAS scores from 3.1 to 3.7 (p<0.05), and VAS scores for pain from 7.8 to 1.5 (p<0.01). However, outcomes were significantly worse in patients who had undergone a prior marrow stimulation procedure (see Table 1).

Table 1. Results at 7-Year Follow-Up

Outcomes	AOFAS Score (SD)	Tegner Activity Scale Score (SD)	VAS Score (SD)
Repeat procedure	62.0 (16.4)	2.0 (1.9)	3 (3.2)
Initial procedure	87.0 (15.0)	4.6 (2.2)	0.6 (1.1)
P Value	<0.01	<0.01	<0.01

AOFAS: American Orthopedic Foot & Ankle Society; VAS: visual analog scale.

Observational Studies

Osteochondral autografting for OCD was also reported by Hangody et al. (2001) for 36 consecutive patients. (6) Most patients had previous surgical interventions and presented with stage III or IV lesions (completely detached or displaced fragment). The average size of the defect was 1 cm, and the average number of grafts per patients was 3 (range, 1-6). At a mean follow-up of 4.2 years, ankle function measured using the Hannover scoring system showed good-to-excellent results in 34 (94%) cases. Examination by radiograph, computed tomography (CT), and MRI showed incorporation into the recipient bed and congruency of the articular surface.

In 2006, Kreuz et al. reported on outcomes from a prospective series of 35 patients who underwent osteochondral grafting from the ipsilateral talar articular facet following failed bone marrow stimulation. (45) Mean lesion diameter was 6.3 mm. At a mean follow-up of 49 months (range, 33-77 months), the AOFAS Ankle-Hindfoot Score had improved from 54.5 points (range, 47-60 points) to 89.9 points (range, 80-100 points).

In 2016, Georgiannos et al. reported on 5- to 7-year follow-up for a prospective cohort of 46 patients who had failed a prior marrow stimulation procedure. (46) Osteochondral plugs, which ranged from 4.75 to 8 mm in diameter, were taken from the talar facet. A temporary block of bone was removed to provide access to the talar dome. At a median follow-up of 5.5 years (range, 52-75 months), AOFAS score (standard deviation) had improved from 55 (4.2) to 90 (5.8), and the median VAS score improved from 52/100 (6.6) to 91 (8.2). All grafts had incorporated and osteotomy sites healed, although 5 patients underwent subsequent surgery for osteophytes.

<u>Subsection Summary: Osteochondral Autograft for Articular Cartilage Lesions of the Ankle That Have Failed a Prior Marrow Stimulation Procedure</u>

The evidence for AOT in patients with articular cartilage lesions of the talus that have failed a prior marrow stimulation procedure includes 2 nonrandomized comparative trials and case series. A nonrandomized comparative study has suggested improved outcomes with AOT compared to repeat marrow stimulation. However, another study has suggested that outcomes may be diminished when AOT is used for a revision procedure compared to primary treatment. Case series have indicated good-to-excellent results of AOT at mid-term follow-up.

Fresh Osteochondral Allograft for Articular Cartilage Lesions of the Ankle

Use of AOT is limited by the number of cores that can be taken from the non-weight-bearing part of the talus or ipsilateral knee. AOT may also be inadequate due to lesion depth or location, such as on the talar shoulder. For osteochondral lesions for which AOT would be inadequate due to lesion size, depth, or location, the use of fresh osteochondral allografts has been reported. Use of fresh allografts for defects of the talus has been reported mainly in case series and a systematic review of these series. Due to the relatively rare occurrence of this condition, most series have fewer than 20 patients. One RCT was identified that compared AOT to allograft plugs for recurrent cartilage lesions.

<u>Systematic Reviews</u>

In a 2017 systematic review, VanTienderen et al. included 5 studies with a total of 90 patients (91 ankles) who received a fresh osteochondral allograft for osteochondral lesions of the talus. (47) Studies selected reported at least 1 outcome of interest, including AOFAS score, Foot Functional Index score, VAS score, reoperation rate, or rate of allograft collapse. The mean lesion volume was 3.7 cm^3 (range, 1.0-10.9 cm^3) and the number of prior procedures ranged from 1 to 4. At a mean follow-up of 45 months (range, 6-91 months), AOFAS scores improved from 48 to 80 and VAS scores improved from 7.1 to 2.7. However, some failures occurred: 23 (25.3%) patients required at least 1 reoperation and 12 (13.2%) patients were considered failures, defined as postoperative graft nonunion or resorption or persistence of symptoms leading to arthrodesis or arthroplasty. In addition to the failure rate of osteochondral allograft transplantation, van Dijk (2017) noted that an osteochondral allograft can compromise a future arthrodesis or arthroplasty by failure of bony ingrowth since the bulk of the graft will consist of dead bone. (48)

<u>Primary Full-Thickness Articular Cartilage Lesions of the Ankle Less Than 1.5 cm^2</u>

Literature on fresh allograft for the treatment of small lesions of the ankle is very limited, because this treatment is considered only when there are no other options available to delay arthrodesis or arthroplasty. Because microfracture is effective as a primary treatment in lesions less than 1.5 cm^2 and AOT is effective as a revision procedure, use of allograft for small lesions has not been reported. Note that other allograft products, such as minced juvenile cartilage and reduced allograft discs, are described in other sections.

<u>Large (Area >1.5 cm^2) or Cystic (Volume >3.0 cm^3) Cartilage Lesions of the Ankle</u>

In 2016, Ahmad and Jones compared osteochondral autograft with fresh allograft plugs for the treatment of large (area >1.5 cm^2, n=9) or recurrent (volume >3.0 cm^3; n=27) cartilage lesions of the talus. (49) Because they only treated 5 patients with large lesions with autograft and 4 patients with large lesions with allograft, comparing treatments in this trial is limited.

<u>Revision of Large (Area >1.5 cm^2) or Cystic (Volume >3.0 cm^3) Osteochondral Lesions of the Ankle</u>

Randomized Trials

The 2016 study by Ahmad and Jones included 9 large and 27 recurrent osteochondral lesions of the talus. (49) Most patients had failed a prior microfracture. The study randomized 20 patients to AOT and 20 patients to plugs taken from a size-matched donor talus. Four patients from the allograft group had significant damage of the shoulder of the talar dome. These 4 received a hemi-talus allograft and were excluded from the study. Foot and Ankle Ability Measures and VAS scores were similar in the 2 groups. In the allograft group, the mean Foot and Ankle Ability Measures score increased from 55.2 to 80.7 and the mean VAS score decreased from 7.8 to 2.7 at final follow-up. These outcomes were reported as being lower than those reported for the autograft group, but the difference was not statistically significant (numerical results were reported separately for anterior and medial approach). More patients in the allograft group had graft nonunion (3/16 [18.8%] patients) vs the autograft group (2/20 [10%] patients), consistent with the systematic review by VanTienderen et al. (described above).

<u>Section Summary: Fresh Osteochondral Allograft for Articular Cartilage Lesions of the Ankle</u>

The evidence on osteochondral allografts for articular cartilage lesions of the ankle includes an RCT, case series and a systematic review of case series. There is little evidence on fresh osteochondral allografts for the primary treatment of full-thickness articular cartilage lesions of the ankle less than 1.5 cm^2. Because microfracture is effective as a primary treatment in lesions less than 1.5 cm^2, AOT is effective as a revision procedure, and allografts have a high failure rate, use of allograft for small primary cartilage lesions is not appropriate.

The evidence on fresh osteochondral allografts for the treatment of large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) osteochondral lesions of the ankle includes a small number of patients in an RCT, case series, and a systematic review of case series. The systematic review found a high failure rate with osteochondral allografts for talar lesions. In addition, use of allografts may have a negative impact on any future arthroplasty or arthrodesis.

The evidence on fresh osteochondral allografts for revision of large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) osteochondral lesions of the ankle includes an RCT. The RCT found that outcomes were slightly, but not significantly, worse with osteochondral allografts compared to autografts. However, failure rates due to nonunion were higher in the allograft group, consistent with other findings.

Osteochondral Autograft for Articular Cartilage Lesions of the Elbow

Systematic Reviews

A 2016 systematic review by Westermann et al. included 24 case series (total N=492 patients) that assessed return to sports after operative treatment for OCD of the capitulum. (50) The most common primary sport was baseball (371/464) followed by gymnastics (35/464). The overall return to sports was 86% at a mean 5.6 months. Average lesion size was similar for the different treatments among 8 studies with information available. Among all 24 studies, patients were more likely to return to their preoperative sport after AOT (0.95; 95% CI, 0.89 to 0.99) compared with débridement or microfracture (0.62; 95% CI, 0.46 to 0.77; p<0.001) or fixation with pins, wires, or screws (0.72; 95% CI, 0.51 to 0.89; p=0.01). Grafts were taken from the lateral femoral condyle or ribs.

Donor-Site Morbidity

Nishimura et al. (2011) evaluated recovery of the donor knee after osteochondral autograft harvesting for capitellar OCD in 12 young athletes (age range, 12-17 years). (51) Pain and function were assessed at 1, 2, 3, 6, 12, and 24 months after surgery. Knee joint effusion persisted in 7 of the 12 patients at 1 month, but none had effusion at 3 months. At 3 months, muscle power of the knee extensor was reduced in 8 patients compared with the preoperative level. At 12 months, 11 patients had reached preoperative knee extensor muscle strength. All patients were pain-free at the donor site by 6 months (mean LKS score, and returned to the previous competitive level of their sport.

Section Summary: Osteochondral Autograft for Articular Cartilage Lesions of the Elbow

OCD of the elbow typically occurs in patients who play baseball or do gymnastics. The literature on AOT for advanced OCD of the elbow consists of small case series, primarily from Europe and Asia, and a systematic review of case series. Although the meta-analysis suggested a benefit of AOT compared to débridement or fixation, further study is needed to determine the effects of the procedure with greater certainty.

Osteochondral Autograft for Articular Cartilage Lesions of Shoulder

A 2009 European study reported 9-year follow-up after AOT for cartilage defects of the shoulder in 7 patients. (52) One additional patient was reported to have had donor-site morbidity at the knee and chose not to return for follow-up. All plugs showed full integration with the surrounding bone, and 6 of 7 patients showed a congruent joint surface. The Constant score improved from 76 points preoperatively to 90 points at 33 months and remained at 91 points at the 9-year follow-up. Subscores for pain and activities of daily living showed significant improvement at 33-month follow-up, with a very slight nonsignificant decline at 9-year follow-up. None of the patients required additional shoulder surgery.

Minced Cartilage for Articular Cartilage Lesions

<u>Autologous Minced Cartilage</u>

In 2011, Cole et al. reported on a multicenter trial with 29 patients (of 582 screened) randomized in a 1:2 ratio to microfracture or Cartilage Autograft Implantation System (CAIS). (53) In the single-stage CAIS procedure, autologous hyaline cartilage was harvested, minced, affixed on a synthetic absorbable scaffold, and fixed on the lesion site with absorbable staples. At baseline, there were no significant differences between groups in the duration of symptoms, ICRS grade, and area and depth of the chondral defect. There was a difference in the sex and work status of the 2 groups. At 3-week and 6-month follow- ups, there were no significant differences in outcomes between the 2 groups, but, at later time points, there were differences reported. The IKDC score was significantly higher in the CAIS group compared with the microfracture group at both 12 (73.9 vs 57.8) and 24 (83.0 vs 59.5) months. All subdomains of the KOOS symptoms and stiffness, pain, activities of daily living, sports and recreation, knee-related quality of life were significantly increased at 24 months in the CAIS group compared with microfracture patients. Qualitative analysis of MRI at 3 weeks and 6, 12, and 24 months showed no differences in fill of the graft bed, tissue integration, or presence of subchondral cysts. Adverse events were similar for the 2 groups.

<u>Allogeneic Juvenile Minced Cartilage</u>

Knee

Evidence on the efficacy of DeNovo NT is limited to case reports and small case series. The largest series identified was an industry-sponsored prospective study by Farr et al. (2014), which included 25 patients with cartilage lesions of the femoral condyle or trochlea. (54) Patients had symptomatic, focal, contained chondral lesions of the femoral condyles or trochlea with defect areas ranging between 1 cm^2 and 5 cm^2 (mean, 2.7 cm^2; range 1.2-4.6 cm^2). Mean number of prior surgeries was 1.1, with 18 patients reporting prior débridement and/or microfracture. Patients returned for follow-up at 3, 6, 12, 18, and 24 months for radiographs, IKDC examination, and completion of questionnaires. Outcomes included the KOOS, IKDC, Marx Activity Scale, and 100-mm VAS score for pain. IKDC score improved over the 24 months of follow-up. At 24 months, IKDC score had improved from 45.7 preoperatively to 73.6 of 100.

There were also significant improvements in KOOS subscores (p<0.001) and VAS pain score (from 43.7/100 at baseline to 11.1 at 24 months, p<0.001). MRI showed a mean lesion fill of 109.7% with mild graft hypertrophy identified in 20.7% of patients. Of 11 elective second-look arthroscopies at 24 months, 2 grafts (18%) showed either partial or complete delamination. Histology from 8 patients with biopsy showed a mixture of hyaline and fibrocartilage; areas with hyaline cartilage varied across sections. There was good integration with the surrounding native cartilage.

A 2013 study included 13 patients (15 knees) who received particulated juvenile allograft to the patella. (55) Ten of the 15 knees underwent concomitant procedures, limiting interpretation of functional outcomes. Cartilage repair assessed at a mean of 28.8 months was reported to be nearly normal in 73% of knees while 27% of knees had evidence of graft hypertrophy. Currently available evidence is insufficient to evaluate the effect of this technology on health outcomes.

Ankle

One proposed advantage of particulated articular cartilage for osteochondral lesions of the talus is that it is not always necessary to perform an osteotomy to access the lesion. At this time, use of DeNovo NT for the talus has been reported in case reports, small case series, and a systematic review of these studies.

In 2017, Saltzman et al. reported a descriptive systematic review of the published case reports and case series. (56) Included were data on 33 ankles from 2 case reports, a series of 7 patients by Bleazy and Brigido (2012) (57) and a series of 24 ankles by Coetzee et al. (2013), (58) described next.

The largest series is from a preliminary report of a larger study by Coetzee et al. (58) In this preliminary report, 24 ankles (23 patients) with osteochondral lesions of the talus (mean lesion size, 125 mm^2); SD=75) were treated with DeNovo NT. Fourteen (58%) of the ankles had failed at least 1 prior bone marrow stimulation procedure. At an average follow-up of 16.2 months, 78% of ankles had good-to- excellent scores on the AOFAS ankle-hindfoot score, with a final mean VAS score of 24 out of 100. However, 18 (76%) ankles had at least 1 concomitant procedure (hardware removal and treatment for impingement, synovitis, instability, osteophytes, malalignment), limiting interpretation of the functional results. One treatment failure was caused by partial graft delamination.

In addition to their systematic review of the literature, Saltzman et al. also reported on 6 patients who had been treated at their institution with particulated juvenile articular cartilage for articular cartilage lesions of the talus. (56) Lesion size ranged from 96 to 308 mm^2. Two of the 6 patients underwent a medial malleolar osteotomy to access the lesion. Implantation procedures included débridement, marrow stimulation, and fixation of the particulated cartilage with fibrin glue. At a mean 13-month follow-up, all 6 patients reported subjective improvements in pain and function. However, for all 3 patients who had MRI between 3 months and 2 years postoperatively, there was persistent subchondral edema and nonuniform chondral surface.

The evidence on autologous minced cartilage includes 1 small RCT from 2011. The evidence on allogeneic minced cartilage includes case reports and case series. The case series have suggested an improvement in outcomes compared with baseline, but there is also evidence of subchondral edema, nonuniform chondral surface, graft hypertrophy, and delamination. For articular cartilage lesions of the knee, further evidence, preferably from RCTs, is needed to evaluate the effect on health outcomes compared with other available procedures. For articular cartilage lesions of the ankle, there are few treatment options and, in the largest case series, over half of the patients had failed prior marrow stimulation. However, the concomitant procedures performed in that study limited interpretation of its results. A randomized comparison with microfracture in patients who have not received prior treatment would permit greater certainty about the effectiveness of this procedure.

Decellularized Osteochondral Allograft

The first report of use of decellularized osteochondral allograft plugs (Chondrofix) was published by Farr et al. in 2016. (59) Review of records for 32 patients identified high failure rates. With failure defined as structural damage of the graft identified by MRI or arthroscopy, or any reoperation resulting in removal of the allograft, 23 (72%) of 32 knees were considered failures.

Reduced Osteochondral Allograft Discs

The evidence on reduced osteochondral allograft discs is limited to case reports and very small case series with 2 to 3 patients. This evidence is insufficient to evaluate the effects of these products on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01347892[a]	Post Market, Longitudinal Data Collection Study of Articular Cartilage Lesions in the Ankle Treated with DeNovo (R) NT	205	Sep 2019
NCT01329445[a]	Post Market, Longitudinal Data Collection Study of DeNovo NT for Articular Cartilage Defects of the Knee	200	Dec 2019

NCT01670617[a]	A Stratified, Post-Market Study of DeNovo NT for the Treatment of Femoral and Patellar Articular Cartilage Lesions of the Knee	254	Dec 2021
Unpublished			
NCT01410136[a]	A Post Market Study to Evaluate the Chondrofix® Osteochondral Allograft Utilized for Treatment of Subjects With Cartilage Lesions in the Knee	29	Terminated (enrollment)

Table Key:

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

American Academy of Orthopaedic Surgeons (AAOS)

In 2010 guidelines, which remain available on the AAOS website in 2017, on the diagnosis and treatment of osteochondritis dissecans (OCD), AAOS was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable OCD lesion. (60, 61)

A 2010 AAOS review of articular cartilage restoration methods stated that "osteochondral autografting is generally used for smaller focal lesions of the femoral condyle no greater than 1.5 to 2 cm." (62)

National Institute for Health and Care Excellence (NICE)

NICE conducted a 2005 review of mosaicplasty for knee cartilage defects. The corresponding guidance, released in 2006, stated that "There is some evidence of short-term efficacy, but data on long-term efficacy are inadequate." (63)

Summary of Evidence

Knee Lesions

For individuals who have full-thickness articular cartilage lesions of the knee who receive osteochondral autografts, the evidence includes randomized controlled trials (RCTs), systematic reviews of RCTs, and longer term observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several systematic reviews have evaluated osteochondral autografting for cartilage repair in the short and mid-term. Compared to abrasion

techniques (e.g., microfracture, drilling), there is evidence that osteochondral autografting decreases failure rates and improves outcomes in patients with medium-size lesions (e.g., 2-6 cm^2) when measured at longer follow-up. This is believed to be due to the higher durability of hyaline cartilage compared to fibrocartilage from abrasion techniques. There appears to be a relatively narrow range of lesion size for which osteochondral autografting is most effective. The best results have also been observed with lesions on the femoral condyles, although treatment of lesions on the trochlea and patella may also improve outcomes. Correction of malalignment is important for success of the procedure. The evidence suggests that osteochondral autografts may be considered an option for moderate-sized symptomatic full-thickness chondral lesions of the femoral condyle, trochlea, or patella. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have full-thickness articular cartilage lesions of the knee when autografting would be inadequate due to lesion size, location, or depth who receive fresh osteochondral allografts, the evidence includes case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Due to the lack of alternatives, this procedure may be considered a salvage operation in younger patients for full-thickness chondral defects of the knee caused by acute or repetitive trauma when other cartilage repair techniques (e.g., microfracture, osteochondral autografting, autologous chondrocyte implantation) would be inadequate due to lesion size, location, or depth. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ankle Lesions

For individuals who have primary full-thickness articular cartilage lesions of the ankle less than 1.5 cm^2 who receive an osteochondral autograft, the evidence includes observational studies and a systematic review of these studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A systematic review found similar improvements in outcomes following microfracture or autologous osteochondral transplantation (AOT) Given the success of marrow stimulation procedures for smaller lesions (<1.5 cm^2) and the increase in donor-site morbidity with graft harvest from the knee, current evidence does not support the use of AOT as a primary treatment for smaller articular cartilage lesions of the ankle. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) full-thickness articular cartilage lesions of the ankle who receive an osteochondral autograft, the evidence includes an RCT and 2 observational studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. An RCT in patients with large lesions found similar efficacy for AOT, marrow stimulation, and arthroplasty at 2-year follow-up. Longer term results were not reported. Because observational studies of marrow stimulation in the talus have generally reported worse outcomes and high failure rates for large lesions, there is a strong rationale for using autografts.

However, there is limited evidence that osteochondral autografts lead to better outcomes than microfracture at longer follow-up. The strongest evidence is derived from 1 observational study that showed good improvement on the Foot and Ankle Outcome Score through at least 5-year follow-up using AOT in both larger (2 plugs) and smaller (1 plug) lesions. Additional study is needed to evaluate the durability of AOT in larger lesions. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have osteochondral lesions of the ankle that have failed primary treatment who receive an osteochondral autograft, the evidence includes 2 nonrandomized comparative trials and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The best evidence for revision AOT comes from a nonrandomized comparative study that found better outcomes with AOT than with repeat marrow stimulation. This finding is supported by case series that have indicated good-to-excellent results at mid-term and longer term follow-up with revision AOT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary full-thickness articular cartilage lesions of the ankle less than 1.5 cm^2 who receive a fresh osteochondral allograft, there is little evidence. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Because microfracture is effective as a primary treatment for lesions less than 1.5 cm^2 and AOT is effective as a revision procedure, use of allograft for small primary cartilage lesions has not been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have large (area >1.5 cm^2) or cystic (volume >3.0 cm^3) cartilage lesions of the ankle when autografting would be inadequate who receive a fresh osteochondral allograft, the evidence includes a small number of patients in an RCT, case series, and a systematic review of case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review found a significant failure rate with osteochondral allografts for talar lesions. Although there is a potential to delay or avoid arthrodesis or total ankle arthroplasty in younger patients, use of an allograft may be detrimental to future treatments. Additional study is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have revision osteochondral lesions of the ankle when autografting would be inadequate who receive a fresh osteochondral allograft, the evidence includes an RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The RCT found that outcomes were slightly, but not significantly, worse with osteochondral allografts than with autografts. However, failure due to nonunion was higher in the allograft group, consistent with other reports. The evidence is insufficient to determine the effects of the technology on health outcomes.

Elbow Lesions

For individuals who have full-thickness articular cartilage lesions of the elbow who receive an osteochondral autograft, the evidence includes a meta-analysis of case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Osteochondritis dissecans of the elbow typically occurs in patients who play baseball or do gymnastics. The literature on osteochondral autografts for advanced osteochondritis dissecans of the elbow consists of small case series, primarily from Europe and Asia, and a systematic review of case series. Although the meta-analysis suggested a benefit of osteochondral autographs compared to débridement or fixation, RCTs are needed to determine the effects of the procedure with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

Shoulder Lesions

For individuals who have full-thickness articular cartilage lesions of the shoulder who receive an osteochondral autograft, the evidence includes a case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Evidence on osteochondral autografting for the shoulder is very limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

Knee, Ankle, Elbow, or Shoulder Lesions

For individuals who have full-thickness articular cartilage lesions of the knee, ankle, elbow, or shoulder who receive autologous or allogeneic minced articular cartilage, the evidence includes a small RCT and small case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment- related morbidity. The evidence on autologous minced cartilage includes 1 small RCT from 2011. The evidence on allogeneic juvenile minced cartilage includes a few small case series. The case series have suggested an improvement in outcomes compared with preoperative measures, but there is also evidence of subchondral edema, nonhomogenous surface, graft hypertrophy, and delamination. For articular cartilage lesions of the knee, further evidence, preferably from RCTs, is needed to evaluate the effect on health outcomes compared with other procedures. There are fewer options for articular cartilage lesions of the ankle. However, further study in a larger number of patients is needed to assess the short- and long-term effectiveness of this technology. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have full-thickness articular cartilage lesions of the knee, ankle, elbow, or shoulder who receive decellularized osteochondral allograft plugs or reduced osteochondral allograft discs, the evidence includes small case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single case series on decellularized osteochondral allograft plugs reported delamination of the implants, and high failure rates. Evidence on reduced osteochondral allograft discs consists only of case reports or and very small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

Contract:

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coding:

This service should not be confused with autologous chondrocyte implantation (ACI); however, providers may use 29866 when billing ACI. The claim should be reviewed for osteochondral autografting and allografting when 27416, 29866 or 29867 are billed, as these codes reflect the mosaicplasty procedure(s).

CODING:

Disclaimer for coding information on Medical Policies

Procedure and diagnosis codes on Medical Policy documents are included only as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, device or diagnosis codes in a Medical Policy document has **no** relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a medical policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT/HCPCS/ICD-9/ICD-10 Codes
The following codes may be applicable to this Medical policy and may not be all inclusive.
CPT Codes
27415, 27416, 28446, 29866, 29867
HCPCS Codes
None

ICD-9 Diagnosis Codes
Refer to the ICD-9-CM manual
ICD-9 Procedure Codes
Refer to the ICD-9-CM manual
ICD-10 Diagnosis Codes
Refer to the ICD-10-CM manual
ICD-10 Procedure Codes
Refer to the ICD-10-CM manual

Medicare Coverage:

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

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Policy History:

Date	Reason
7/15/2018	Reviewed. No changes, other than editorial addition of the word "particulated" to the following coverage statement: "Treatment of focal articular cartilage lesions with autologous minced/particulated cartilage is considered experimental, investigational and/or unproven. Intent of coverage did not change."
2/1/2018	Document updated with literature review. The following changes were made to Coverage: 1) Added conditional coverage for osteochondral allografting and autografting of the talus; and 2) Added statement considering treatment of focal articular cartilage lesions with decellularized osteochondral allograft plugs (e.g., Chondrofix) to be experimental, investigational and/or unproven; and 3) Added statement considering treatment of focal articular cartilage lesions with reduced osteochondral allograft discs (e.g., ProChondrix, Cartiform) to be experimental, investigational and/or unproven.
4/15/2017	Reviewed. No changes.
12/15/2016	Document updated with literature review. The following was added to the medical necessity statement for osteochondral allografting: "when other cartilage repair techniques (e.g., microfracture, osteochondral autografting or autologous chondrocyte implantation) would be inadequate due to the size, location, or depth of the lesion." The following was added to the medical necessity statement for osteochondral autografting: "in patients who have had an inadequate response to a prior surgical procedure" and to criterion regarding surrounding articular cartilage to state, "Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect." Clarification wording was added to the medically necessary coverage statement and criteria.

2/1/2015   Document updated with literature review. The following was added to Coverage: 1) Addition to criteria to include Outerbridge grade III when lesion is discrete, single, unipolar, and full thickness; 2) NOTE - Osteochondral autograft or allograft transplantation may be medically necessary when performed in combination, either concurrently or sequentially, with meniscal allotransplantation for focal articular cartilage lesions; 3) NOTE - Additional procedures, such as repair of ligaments or tendons of an osteotomy for realignment (includes misalignment and instability) may be performed at the same time of the osteochondral autografting or allografting procedure; and 4) Treatment of focal articular cartilage lesions with autologous and/or allogeneic minced cartilage is considered experimental, investigational and/or unproven. Description, Rationale, and References substantially revised and reorganized. "Osteochondral" removed from the policy title.

2/15/2010   Revised/updated entire document, osteochondral autografting and allografting remain conditional based on medical necessity criteria. This policy is no longer scheduled for routine literature review and update.

1/1/2008   New CPT/HCPCS code added

8/15/2007   Revised/updated entire document

1/1/2005   Revised/updated entire document, originated from position statement

12/18/2001   New medical document

Archived Document(s):

Title:	Effective Date:	End Date:
Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	02-01-2018	07-14-2018
Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	04-15-2017	01-31-2018
Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	12-15-2016	04-14-2017
Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	02-01-2015	12-14-2016

Osteochondral Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	02-15-2010	01-31-2015
Osteochondral Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	08-15-2007	02-14-2010
Osteochondral Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions	01-01-2005	08-14-2007
Osteochondral Grafts in the Treatment of Articular Cartilage Lesions	12-18-2001	12-31-2004